

# Exercise performance in patients with peripheral arterial disease who have different types of exertional leg pain

Andrew W. Gardner, PhD,<sup>a,c,d</sup> Polly S. Montgomery, MS,<sup>a,c,d</sup> and Azhar Afaq, MD,<sup>b</sup> *Oklahoma City, Okla; and Baltimore, Md*

**Objective:** This study compared the exercise performance of patients with peripheral arterial disease (PAD) who have different types of exertional leg pain.

**Methods:** Patients with PAD were classified into one of four groups according to the San Diego Claudication Questionnaire: intermittent claudication (n = 406), atypical exertional leg pain causing patients to stop (n = 125), atypical exertional leg pain in which patients were able to continue walking (n = 81), and leg pain on exertion and rest (n = 103). Patients were assessed on the primary outcome measures of ankle-brachial index (ABI), treadmill exercise measures, and ischemic window.

**Results:** All patients experienced leg pain consistent with intermittent claudication during a standardized treadmill test. The mean ( $\pm$  SD) initial claudication distance (ICD) was similar ( $P = .642$ ) among patients with intermittent claudication ( $168 \pm 160$  meters), atypical exertional leg pain causing patients to stop ( $157 \pm 130$  meters), atypical exertional leg pain in which patients were able to continue walking ( $180 \pm 149$  meters), and leg pain on exertion and rest ( $151 \pm 136$  meters). The absolute claudication distance (ACD) was similar ( $P = .648$ ) in the four respective groups ( $382 \pm 232$ ,  $378 \pm 237$ ,  $400 \pm 245$ , and  $369 \pm 236$  meters). Similarly, the ischemic window, expressed as the area under the curve (AUC) after treadmill exercise, was similar ( $P = .863$ ) in these groups ( $189 \pm 137$ ,  $208 \pm 183$ ,  $193 \pm 143$ , and  $199 \pm 119$  AUC).

**Conclusion:** PAD patients with different types of exertional leg pain, all limited by intermittent claudication during a standardized treadmill test, were remarkably similar in ICD, ACD, and ischemic window. Thus, the presence of ambulatory symptoms should be of primary clinical concern in evaluating PAD patients regardless of whether they are consistent with classic intermittent claudication. (*J Vasc Surg* 2007;46:79-86.)

Symptomatic peripheral arterial disease (PAD), which affects 6% of the American population  $>55$  years old,<sup>1</sup> is a leading cause of morbidity.<sup>2</sup> Patients experience lower extremity pain during ambulation because the impaired circulation cannot meet the energy needs of the active musculature. As a consequence, these patients have ambulatory dysfunction,<sup>3-6</sup> decline in other domains of physical function,<sup>7-10</sup> lower daily physical activity,<sup>11</sup> impaired health-related quality of life,<sup>12,13</sup> and difficulty in completing activities of daily living that require the use of the lower extremities.<sup>14</sup>

A widely recognized symptom of PAD is intermittent claudication, defined as ischemic calf pain that occurs dur-

ing ambulation and resolves  $\leq 10$  minutes of rest.<sup>15</sup> However, patients with PAD are often asymptomatic or have symptoms that are atypical from the classic description of intermittent claudication.<sup>16-18</sup> Recent studies have compared PAD patients with different types of exertional leg pain on various measures of functional status.<sup>19-21</sup> Patients with intermittent claudication have worse functional status, self-reported ambulatory function, and health-related quality of life than patients with atypical pain,<sup>21</sup> but better values than those reporting leg pain on exertion and rest.<sup>20,21</sup> These measures, which are either subjective or are based on self-paced exercise tasks, do not provide the level of standardization as does a treadmill test to compare claudication distances and peripheral vascular function among groups with different types of exertional pain.

To our knowledge, no study to date has examined exercise performance and peripheral hemodynamic responses in these patients during a standardized treadmill test. Thus, the primary purpose of this study was to compare the exercise performance of patients with PAD who have different types of exertional leg pain. An additional aim was to compare secondary measures, such as physical function, physical activity, health-related quality of life, and peripheral vascular reactivity, in patients with different types of exertional leg pain.

## METHODS

**Screening.** A total of 905 PAD patients with symptoms of leg pain were evaluated in the Geriatrics, Research,

From CMRI Metabolic Research Center<sup>a</sup> and Department of Medicine, Cardiovascular Section,<sup>b</sup> University of Oklahoma Health Sciences Center; Department of Medicine, Division of Gerontology, University of Maryland,<sup>c</sup> and Maryland Veterans Affairs Health Care System.<sup>d</sup>

Competition of interest: none.

Dr Gardner was supported by grants from the National Institute on Aging (NIA) (R01-AG-16685, K01-00657), by a Claude D. Pepper Older American Independence Center grant from NIA (P60-AG12583), by a Geriatric, Research, Education, and Clinical Center grant (GRECC) from the Veterans Affairs Administration, and by a National Institutes of Health, National Center for Research Resources, General Clinical Research Center grant (M01-RR-14467).

Reprint requests: Andrew W. Gardner, PhD, CMRI Hobbs-Recknagel Professor, General Clinical Research Center, University of Oklahoma Health Sciences Center, 1122 NE 13th St, ORI-W 1400, Oklahoma City, OK 73117 (e-mail: [andrew-gardner@ouhsc.edu](mailto:andrew-gardner@ouhsc.edu)).

0741-5214/\$32.00

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doi:10.1016/j.jvs.2007.02.037

Education, and Clinical Center at the Maryland Veterans Affairs Health Care System (MVAHCS) at Baltimore. Patients were recruited from the vascular clinic at the site of the Baltimore MVAHCS and from advertisements. Patients were included if they had Fontaine stage II PAD,<sup>22</sup> defined by the inclusion criteria of a history of leg pain, ambulation during a graded treadmill test limited by leg pain,<sup>23</sup> and an ankle-brachial index (ABI) at rest of  $<0.90$ .<sup>1</sup> Patients were excluded for absence of PAD (ABI  $\geq 0.90$ ), inability to obtain an ABI measure due to noncompressible vessels, asymptomatic PAD (Fontaine stage I), use of medications indicated for the treatment of intermittent claudication (cilostazol and pentoxifylline)  $\leq 3$  months before investigation, exercise tolerance limited by factors other than leg pain (eg, severe coronary artery disease, dyspnea, poorly controlled blood pressure), and active cancer, renal disease, or liver disease.

A total of 715 patients were deemed eligible for this investigation, and 190 patients were ineligible. All patients lived independently at home and completed all of the assessments described below in  $\leq 1$  week. The Institutional Review Boards at the University of Maryland and the MVAHCS at Baltimore approved the procedures used in this study. Written informed consent was obtained from each patient before investigation.

**Exertional leg symptom groups.** Leg symptoms were evaluated by administering the San Diego Claudication Questionnaire,<sup>24</sup> a standardized and validated 11-item questionnaire based on the Rose questionnaire for intermittent claudication.<sup>15</sup> According to the responses from the San Diego Claudication Questionnaire, PAD patients were placed into one of the four exertional leg symptom groups: (1) leg pain on exertion that sometimes begins at rest (leg pain on exertion and rest group,  $n = 103$ ), (2) leg pain on exertion that does not begin at rest, causes the patient to stop or slow down, but does not fulfill the remaining criteria for intermittent claudication (atypical exertional leg pain/stop group,  $n = 125$ ), (3) leg pain on exertion that does not begin at rest and does not cause the patient to stop or slow down (atypical exertional leg pain/carry-on group,  $n = 81$ ), and (4) leg pain on exertion that does not begin at rest, causes the patient to stop or slow down, is located in the calves, does not resolve while walking, and goes away  $\leq 10$  minutes of rest (intermittent claudication group,  $n = 406$ ).<sup>19,20,21,25,26</sup>

**Medical history.** Demographic information, height, weight, cardiovascular risk factors, comorbid conditions, claudication history, and a list of current medications were obtained during a physical examination and medical history interview to begin the evaluation.

**Claudication distances and peak oxygen uptake.** Patients performed a progressive, graded treadmill protocol (2 miles/hour, 0% grade with 2% increase every 2 minutes) until maximal claudication pain, as previously described.<sup>23</sup> The initial claudication distance (ICD), absolute claudication distance (ACD), time to relief of claudication pain after the test, and peak oxygen uptake were measured. The test-retest intraclass reliability coefficient with these proce-

dures is  $R = 0.89$  for ICD,<sup>23</sup>  $R = 0.93$  for ACD<sup>23</sup>, and  $R = 0.88$  for peak oxygen uptake.<sup>27</sup>

**Walking economy and fractional utilization.** Oxygen uptake was measured during a constant, submaximal work rate at a treadmill speed of 2 miles/hour and a grade of 0% until maximal claudication pain, or for a maximum of 20 minutes.<sup>28</sup> Walking economy was measured as the oxygen uptake obtained during the final minute of the test. To quantify the intensity of the walking economy test as a percentage of peak capacity, fractional utilization was calculated as the walking economy oxygen uptake/peak oxygen uptake.

**Ankle-brachial index and ischemic window.** As previously described, the ABI was obtained from the more severely diseased lower extremity by the Doppler ultrasound technique before and at 1, 3, 5, and 7 minutes after each treadmill test.<sup>29</sup> The reduction in ankle systolic blood pressure after treadmill exercise from the resting baseline value was quantified by calculating the area under the curve (AUC), referred to as the ischemic window.<sup>30</sup>

**Six-minute walk distances.** Patients performed an over-the-ground, 6-minute walk test supervised by trained exercise technicians, as previously described.<sup>31</sup> The pain-free and total distance walked during the test were recorded. The test-retest intraclass reliability coefficient is  $R = 0.75$  for the distance to onset of claudication pain, and  $R = 0.94$  for the total 6-minute walking distance.<sup>31</sup>

**Walking Impairment Questionnaire.** Self-reported ambulatory ability was assessed by using Walking Impairment Questionnaire, a validated questionnaire for PAD patients that assesses the subject's ability to walk at various speeds and distances and to climb stairs.<sup>10</sup>

**Short Physical Performance Battery.** The Short Physical Performance Battery score was calculated from the performance of a 4-meter walk test, a chair stand test, and a standing balance test as previously described.<sup>32,33</sup> Briefly, during the 4-meter walk test, walking velocity was assessed by measuring the time required for subjects to walk a distance of 4 meters marked out in a corridor at their usual pace. Patients performed this test twice, and the faster of the two walks was used for analysis. During the chair stand test, lower extremity strength and balance were assessed by performing a repeated chair rise test in which patients completed five sequential sit-to-stand transfers from an armless 18-inch high, straight-backed chair with their arms folded across their chest. During the standing balance test, balance was assessed by measuring the time that patients could hold a stance in side-by-side, semi-tandem, and full-tandem positions.

For each of the three tests, patients were scored on a 0 to 4 ordinal scale, with a score of 0 representing inability to perform the test and scores between 1 and 4 representing quartiles of performance based on normative data on  $>5000$  community-dwelling people published from the Established Populations for the Epidemiologic Studies of the Elderly.<sup>32</sup> The Short Physical Performance Battery score ranges from 0 to 12 (0 = worst function, 12 = best function) and is predictive of mobility loss, nursing home

**Table I.** Clinical characteristics of patients with peripheral arterial disease placed in four exertional leg symptom groups\*

Variables	Leg pain group on exertion and rest group (n = 103)	Atypical exertional leg pain groups		Intermittent claudication group (n = 406)	P
		Stop (n = 125)	Carry on (n = 81)		
Age (years)	67 ± 7	69 ± 9	68 ± 9	68 ± 8	.858
Weight (kg)	82.4 ± 16.8	83.0 ± 16.3	80.9 ± 16.7	82.1 ± 15.1	.344
Body mass index (kg/m <sup>2</sup> )	28.1 ± 5.0	28.2 ± 4.9	27.5 ± 5.0	28.4 ± 4.5	.200
Ankle-brachial index	0.71 ± 0.19	0.68 ± 0.21	0.69 ± 0.23	0.68 ± 0.22	.429
Leg pain duration (years)	4.5 ± 5.2	5.3 ± 6.7	4.9 ± 6.2	4.6 ± 4.8	.531
Sex (% men)	78	82	86	79	.252
Race (% white)	59	58	59	65	.621
Current smoking	33	32	37	36	.403
Diabetes	35	32	36	38	.745
Hypertension	65	61	64	66	.298
Hyperlipidemia	43	43	39	45	.637
Abdominal obesity	44	38	35	39	.346
Obesity <sup>†</sup>	37	32	33	35	.521

\*Continuous values are presented as means ± SD; categorical variables are presented as percentages.

<sup>†</sup>Obesity was defined as having a body mass index >30 kg/m<sup>2</sup>.

placement, and mortality among community-dwelling elderly individuals.<sup>32,33</sup> The test-retest intraclass reliability coefficient is  $R = 0.93$  for the Short Physical Performance Battery score.<sup>34</sup>

**Self-perceived health.** The Health Utilities Index, ranging between 0 (the worst imaginable health) and 100 (the best imaginable health), was used to assess self-reported health, as previously described.<sup>35</sup> Patients were asked to select a numeric value on the scale that best corresponded to their current overall health state.

**Daily physical activity.** Physical activity level was monitored over two consecutive weekdays by a Caltrac accelerometer (Muscle Dynamics, Torrance, Calif) attached to the belt of each subject, as previously described.<sup>36</sup> In addition, a physical activity scale was used to assess the self-reported physical activity level over the preceding month, as previously described.<sup>11,37</sup> The accelerometer measure of physical activity has a test-retest intraclass reliability coefficient of  $R = 0.84$ <sup>37</sup> and provides a valid estimate of daily physical activity assessed by the gold standard technique of doubly labeled water.<sup>36</sup>

**Quality of life.** Health-related quality of life was assessed with the Medical Outcomes Study Short-Form 36 (MOS SF-36) General Health Survey.<sup>38</sup> The MOS SF-36 is a reliable and valid generic instrument that includes multi-item scales measuring the eight health domains of physical function, role limitations due to physical problems, general health, bodily pain, social function, role limitations due to emotional problems, mental health, and vitality. For each subscale, item scores were recorded, summed, and standardized into a scale from 0 to 100, with better health states resulting in higher scores.

**Calf blood flow.** Calf blood flow was obtained at rest and after 3 minutes of arterial occlusion (ie, reactive hyperemia) in the more severely diseased leg using venous occlusion mercury strain-gauge plethysmography, as previously described.<sup>39</sup> The test-retest intraclass reliability coefficient is  $R = 0.86$  for calf blood flow.<sup>39</sup>

**Transcutaneous oxygen tension.** Transcutaneous oxygen tension (TcPo<sub>2</sub>) was measured at rest and after 3 minutes of arterial occlusion on the medial portion of the calf musculature of the more affected leg with a Clark-type polarographic electrode and a TcPo<sub>2</sub> Monitor (Novamatrix Medical System, Model 818, Wallingford, Conn). The change in calf TcPo<sub>2</sub> after arterial occlusion is a measure of the ischemic response to this test. The test-retest intraclass reliability coefficient is  $R = 0.87$  for calf TcPo<sub>2</sub>.<sup>27</sup>

**Statistical analyses.** One-factor analysis of variance (ANOVA) and  $\chi^2$  tests were used to assess whether differences in clinical characteristics existed among the four groups of PAD patients with exertional leg symptoms. All of the ANOVA tests met the assumption of having normally distributed data. A significant main effect in the ANOVA was followed by Tukey post hoc comparisons to compare pair-wise differences among the group means. All analyses were performed using SPSS-PC statistical software (SPSS Inc, Chicago, Ill). Statistical significance was set at  $P < .05$ . Measurements are presented as means ± standard deviations.

## RESULTS

Patients with PAD were classified into four groups according to their exertional leg pain. The clinical characteristics of these groups are summarized in Table I. The ABI and duration of leg pain were similar ( $P > .005$ ) in all groups. The groups were also similar with respect to age, sex, racial composition, current smoking status, cardiovascular risk factors, and measures of body mass.

The measurements obtained during standardized treadmill tests in the patients with PAD are listed in Table II. All patients experienced exertional leg pain during the treadmill tests. The pain was consistent with intermittent claudication, because walking was discontinued due to calf leg pain that resolved during subsequent rest. The ICD, ACD, time to relief of claudication pain, and peak oxygen uptake values obtained from the

**Table II.** Treadmill measurements of patients with peripheral arterial disease placed in four exertional leg symptom groups\*

Variables	Leg pain on exertion and rest group (n = 103)	Atypical exertional leg pain groups		Intermittent claudication group (n = 406)	P
		Stop (n = 125)	Carry on (n = 81)		
ICD (meters)	151 ± 136	157 ± 130	180 ± 149	168 ± 160	.642
ACD (meters)	369 ± 236	378 ± 237	400 ± 245	382 ± 232	.648
Time to relief of claudication pain (min:sec)	7:52 ± 4:20	7:21 ± 4:16	6:31 ± 4:15	7:28 ± 4:01	.893
Peak oxygen uptake (mL/[kg · min])	13.9 ± 2.6	14.1 ± 3.0	14.4 ± 3.6	14.8 ± 3.7	.505
Walking economy (mL/[kg · min])	12.3 ± 3.8	12.2 ± 4.6	11.3 ± 2.0	12.0 ± 2.7	.330
Fractional utilization (%)	88 ± 17	87 ± 20	82 ± 16	84 ± 18	.466
Ischemic window After graded treadmill test (AUC)	199 ± 119	208 ± 183	193 ± 143	189 ± 137	.863
After walking economy test (AUC)	122 ± 117	119 ± 114	113 ± 109	112 ± 94	.955

ICD, Intermittent claudication distance; ACD, actual claudication distance; AUC, area under curve.

\*Values are means ± SD.

**Table III.** Physical function, self-reported health, and physical activity level of patients with peripheral arterial disease placed in four exertional leg symptom groups\*

Variables	Leg pain on exertion and rest group (n = 103)	Atypical exertional leg pain groups		Intermittent Claudication Group (n = 406)	P
		Stop (n = 125)	Carry on (n = 81)		
Six-minute walk					
Pain-free distance (meters)	178 ± 128	189 ± 124	196 ± 138	187 ± 131	.922
Distance (meters)	342 ± 94 <sup>†</sup>	385 ± 94	394 ± 106	376 ± 95	.018
WIQ scores					
Distance (%)	30 ± 32	32 ± 33	36 ± 35	33 ± 34	.936
Speed (%)	33 ± 31	34 ± 26	36 ± 30	34 ± 27	.630
Stair climbing (%)	37 ± 33	38 ± 38	41 ± 34	39 ± 35	.702
Short Physical Performance Battery score (units)	9.5 ± 1.9 <sup>†</sup>	10.2 ± 2.0	10.8 ± 2.2	10.1 ± 2.1	.020
Self-Perceived Health (%)	67 ± 17	70 ± 21	75 ± 19	70 ± 19	.172
Physical Activity Scale (units)	1.1 ± 0.9 <sup>†</sup>	1.4 ± 1.2	1.6 ± 1.1	1.5 ± 1.1	.037
Daily Physical Activity (kcal/day)	268 ± 185 <sup>†</sup>	351 ± 194	370 ± 231	337 ± 211	0.049

WIQ, Walking Impairment Questionnaire.

\*Values are means ± SD.

<sup>†</sup>Significantly lower than the other groups ( $P < .008$ ).

progressive, graded treadmill test were similar in the four groups ( $P > .05$ ). The walking economy and fractional utilization measures obtained during treadmill walking were also similar ( $P > .05$ ), as was the ischemic window obtained immediately after both the progressive, graded treadmill test, and the submaximal work-rate treadmill test ( $P > .05$ ).

Physical function, self-reported health, and physical activity levels of patients with PAD placed in four exertional leg pain groups are summarized in Table III. The group

with leg pain on exertion and rest had a shorter 6-minute walking distance, a lower Short Physical Performance Battery score, and lower physical activity values than each of the other three groups ( $P < .05$ ). The pain-free distance during the 6-minute walk test, each score from the Walking Impairment Questionnaire, and self-reported health were similar in the four groups ( $P > .05$ ). Measures of health-related quality of life (Table IV) as well as calf blood flow and transcutaneous oxygen tension (Table V) were also similar ( $P > .05$ ).

**Table IV.** Health-related quality-of-life measurements of patients with peripheral arterial disease placed in four exertional leg symptom groups\*

Variables	Leg pain on exertion and rest group (n = 103)	Atypical exertional leg pain groups		Intermittent claudication group (n = 406)	P
		Stop (n = 125)	Carry on (n = 81)		
Physical Function	49 ± 22	66 ± 16	57 ± 25	55 ± 22	.597
Role Limitations–Physical	63 ± 38	38 ± 35	59 ± 42	57 ± 42	.769
Bodily Pain	54 ± 20	60 ± 22	62 ± 21	57 ± 24	.995
General Health	60 ± 22	68 ± 19	61 ± 22	59 ± 22	.439
Social Function	75 ± 21	83 ± 19	81 ± 22	79 ± 24	.706
Role Limitations–Emotional	67 ± 44	50 ± 36	74 ± 38	67 ± 41	.253
Mental Health	80 ± 15	84 ± 13	77 ± 17	78 ± 16	.724
Vitality	63 ± 22	61 ± 19	62 ± 19	60 ± 21	.539

\*Values are means ± SD.

**Table V.** Peripheral hemodynamic measurements of patients with peripheral arterial disease placed in four exertional leg symptom groups\*

Variables	Leg Pain on exertion and rest group (n = 103)	Atypical exertional leg pain groups		Intermittent claudication group (n = 406)	P
		Stop (n = 125)	Carry on group (n = 81)		
Calf blood flow					
Rest (%/min)	2.82 ± 1.42	3.47 ± 1.57	3.46 ± 1.70	3.59 ± 1.70	.363
Hyperemia (%/min)	8.14 ± 4.87	8.42 ± 3.70	8.84 ± 4.59	9.31 ± 4.18	.200
Change from rest to hyperemia (%)	198 ± 111	161 ± 118	174 ± 125	188 ± 149	.190
Calf TcPo <sub>2</sub>					
Rest (mm Hg)	35 ± 18	40 ± 17	43 ± 16	37 ± 17	.338
Hyperemia (mm Hg)	25 ± 20	31 ± 21	30 ± 32	24 ± 17	.111
Change from rest to hyperemia (%)	–29 ± 31	–23 ± 38	–30 ± 31	–35 ± 28	.240

TcPo<sub>2</sub>, Transcutaneous oxygen pressure.

\*Values are means ± SD.

## DISCUSSION

The major findings of this investigation were (1) all patients experienced symptoms during the treadmill test consistent with classic intermittent claudication, suggesting that patients in the three atypical pain groups are misreporting their symptoms, (2) exercise performance during a standardized treadmill test was similar among all exertional leg pain groups, and (3) physical function and daily physical activity were lowest in patients who reported leg pain on exertion and rest.

To our knowledge, this study is the first to quantify and compare the treadmill exercise performance of PAD patients with different types of exertional leg pain. A key observation was that during a standardized treadmill test, patients who had leg symptoms atypical from classic intermittent claudication were limited in their exercise performance by ischemic leg pain consistent with intermittent claudication, which resolved soon after exercise. The similar walking distances to the onset of leg pain and to maximal tolerable leg pain in all four groups, as well as the similar cardiopulmonary function and walking economy measures, indicate that the PAD symptom subtype had little impact on standardized exercise performance. Finally, the ischemic window values obtained after treadmill exercise confirm

that the exertional leg pain in each group was of vascular origin and that ambulation was limited by peripheral vascular insufficiency to a similar extent regardless of leg pain subtype. Therefore, the stratification of patients into various leg pain subgroups is not useful in distinguishing among patients on standard PAD-related outcome measures such as ICD, ACD, ABI, and the ischemic window.

The similarity in exercise performance in all groups during standardized treadmill exercise suggests that patients who report atypical exertional leg pain should be considered as if they have classic intermittent claudication. As such, these patients should undergo similar medical management even if their description of exertional leg pain does not meet every criterion of classic intermittent claudication.

It is not clear why symptoms vary among claudicant patients. One possibility is that the patients do not fully understand the questions on the San Diego Claudication Questionnaire, and consequently, they misreport their symptoms. The variation may be due to differences in walking patterns in the community setting. For example, to be defined as having classic intermittent claudication on the San Diego Claudication Questionnaire, patients must answer “yes” when asked if they experience leg pain while



walking at an ordinary pace on level ground. Differences in the perception of an ordinary pace and differences in individual walking paces may affect the answer. Patients who perceive an ordinary pace as slow, or who walk slowly at their preferred speed, may be less likely to report leg pain than those who perceive an ordinary pace as fast, or who walk fast.

Differences in walking pace may also affect the patient's response when asked if the leg pain ever disappears while walking. To be defined as having classic intermittent claudication, patients must answer "no," but that answer may depend on whether the walking pace changes after the onset of pain. Patients who slow their walking pace once leg pain occurs may experience pain relief and, consequently, are defined as having atypical pain. These patients may actually have classic intermittent claudication but are simply misclassified because they slow their walking pace to relieve leg pain rather than their pain disappearing in some atypical fashion. In contrast, those who continue walking at the same pace after the onset of leg pain may not experience pain relief as they continue to walk and thus are defined as having classic intermittent claudication. Finally, many patients may not walk enough or be sufficiently attentive to the conditions that produce exertional leg pain to accurately describe their symptoms.

Despite a similar exercise performance and a similar ischemic window response to standardized treadmill exercise in the four groups, the patients with leg pain on exertion and rest had the lowest values for the 6-minute walking distance, Short Physical Performance Battery score, and daily physical activity. The 6-minute walking distance for the patients who reported leg pain on exertion and rest was 34 meters shorter than for patients with intermittent claudication. This supports a previous report showing the former group to have a shorter 6-minute walk distance of 37 meters.<sup>20</sup> The shorter 6-minute walk distance in those with leg pain on exertion and rest compared with those with intermittent claudication cannot be attributed to worse exertional leg pain because both groups had a similar pain-free walking distance during the 6-minute walk test as well as similar ICD and ACD values during a standardized treadmill test. Furthermore, the difference in the 6-minute walk distance between the groups is not due to differences in peripheral vascular insufficiency because the ABI, ischemic window, calf blood flow, and TcPo<sub>2</sub> measures were similar in all groups. In fact, the ABI of patients with leg pain on exertion and rest was higher than in those with intermittent claudication in the previous study.<sup>20</sup>

The lower 6-minute walk distance, Short Physical Performance Battery score, and daily physical activity in patients with leg pain on exertion and rest suggests that they have further impairment in lower extremity muscular endurance and function unrelated to the severity of PAD symptoms and disease severity. Thus, patients who report any pain at rest are more functionally dependent than patients who experience pain only on exertion, regardless of whether the pain is typical of intermittent claudication. It

should be recognized, however, that the patients who reported any pain at rest in the current study did not have more advanced PAD, which would have placed them in a more advanced Fontaine classification stage. Patients with rest pain according to Fontaine stage III PAD typically have ABI values much lower than the patients in this investigation, reflecting more severe chronic ischemia in the lower extremity that eventually leads to tissue loss or gangrene. This was clearly not the case for those who reported having leg pain on exertion and rest and indicates the rest pain was not due to a more advanced level of PAD.

Our study supports previous work that patients with leg pain on exertion and rest have the worst performance on each component of the Short Physical Performance Battery,<sup>20</sup> which includes a prolonged time to complete five sequential sit-to-stand transfers, impaired ability to hold a full tandem stand, and a slower walking velocity over a distance of 4 meters.<sup>20</sup> These differences in physical function may partially explain or be a consequence of the 20% lower monitored physical activity level of the patients with leg pain on exertion and rest compared with those with intermittent claudication as well as the 27% lower self-reported physical activity level. The difference in monitored physical activity is similar to the 21% difference between the groups in a previous report,<sup>20</sup> although this difference was not significant, perhaps due to the smaller group sample sizes than this study.

This study has limitations that deserve mention. The results are generalizable to PAD patients with a history of leg pain and who are limited by leg pain during a standardized treadmill test, regardless of whether the leg pain is typical or atypical of intermittent claudication. Thus, the present findings cannot be generalized to patients with asymptomatic PAD or to those who are limited in their exercise performance by other significant comorbid conditions.

Another limitation is that most of the participants were veterans, and consequently, approximately 80% of the sample was men. However African Americans were well represented in this sample as were patients with typical risk factors for PAD, including smoking, diabetes, hypertension, hyperlipidemia, and obesity. Thus, in patients limited by leg pain, the findings of the present study are generalizable to the large proportion with numerous comorbid conditions.

A final limitation is that the analyses did not control for medications such as statins. We believe, however, that medication usage had minimal influence on the results of this study because the proportion of those with diabetes, hypertension, and hyperlipidemia were remarkably similar among the four leg pain groups.

## CONCLUSION

The clinical relevance of this study is that PAD patients who have leg symptoms atypical from classic intermittent claudication have vascular-mediated limitations in exercise performance during standardized treadmill testing similar to those patients with intermittent

claudication. Thus, any ambulatory symptoms of PAD patients should be viewed as having similar consequences on exercise performance as that of classic intermittent claudication. Although the subtype of exertional leg pain in PAD patients has little impact on standardized exercise performance, it is not clear whether patients with different types of exertional leg pain have different responses to treatment interventions designed to improve ambulatory function. Such intervention trials are needed.

PAD patients with different types of exertional leg pain, all limited by intermittent claudication during a standardized treadmill test, were remarkably similar in ICD, ACD, and ischemic window. Thus, we conclude that the presence of ambulatory symptoms should be of primary clinical concern in evaluating PAD patients regardless of whether they are consistent with classic intermittent claudication.

Appreciation is extended to Dr Steven Blevins for reviewing this manuscript.

#### AUTHOR CONTRIBUTIONS

Conception and design: AG, PM, AA

Analysis and interpretation: AG

Data collection: AG, PM

Writing the article: AG

Critical revision of the article: AG, PM, AA

Final approval of the article: AG, PM, AA

Statistical analysis: AG

Obtained funding: AG

Overall responsibility: AG

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Submitted Oct 31, 2006; accepted Feb 7, 2007.

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